‘‘DESIGN AND DEVELOPMENT OF PEDIATRIC FORMULATIONS OF SECOND LINE ANTITUBERCULOSIS MEDICATIONS’’

A SYNOPSIS

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1.AIM& OBJECTIVE:

The aim of present study is to design and develop Pediatric formulations of second-line anti-tuberculosis medications.

The present study is designed with the following objectives:

1) Preformulation studies to find out the compatibility between the drug and the polymers.
2) Preparation and evaluation of the tablet blend.
3) Formulation of different batches of dispersible tablets.
4) Evaluations of formulated tablets as per pharmacopoeial standards
   - Physiochemical characterization
   - Uniformity of drug content
   - In-Vitro drug release studies
   - Stability study of optimized best formulation.

2.INTRODUCTION

Tuberculosis (TB) is a serious health problem for children globally, causing an estimated 80,000 deaths in HIV-uninfected children and from 0.5-1 million new cases each year (1). Moreover, there is an alarming increase in the number of children with multidrug-resistant (MDR) and extensively drug-resistant (XDR)-TB (2). Unfortunately, the development of pediatric TB medications trails behind those made available to adults. The available orally formulated immediate-release adult-strength tablets were generally not designed for flexible/alternate dosing, so these are difficult to adapt to re-dosing based on age and/or weight, which is customary in children. One common, makeshift solution is to crush tablets normally intended for adults and administer a portion of the powder to the child, a procedure that comes with a number of problems: inaccurate dosing (due to lack of information of what is appropriate), a disruption of the coating (potentially affecting exposure and worsening palatability), improper/imprecise dose administration, and a potential waste of the active pharmaceutical ingredient (API). These problems may worsen adherence, as these drugs are to be taken over a time span of many months, often at home. As ann alternative, some of the second-line TB drugs are provided as liquid solutions or suspension. However these come with their own problems: the containers that contain these are bulky, liquids are generally less stable even when refrigerated, taste-masking is

difficult, storage, packaging and safe transportation are expensive, and caregivers prefer tablet formulations over suspensions for chronic conditions like HIV (3). A third, and now preferred option, as outlined in the general World Health Organization (WHO)/United Nations Children's Fund (UNICEF) new children's medicine guide in 2008 (4) are dispersible tablets, which are dispersed in water prior to intake. Their main advantages are ease of administration, transport, storage and opportunities for taste-masking. One successful example of taste-masking in another condition is Coartem® Dispersible, an anti-malarial developed especially for children as a sweet-tasting, cherry-flavored tablet (www.mmv.org). A second example of taste-masking for pediatric use is a formulation where the solubility of quinine was decreased so that the bulk of this bitter API is released not in the mouth but further in the gastrointestinal tract (5). Another advantage of dispersible tablets is that distinct pill strengths can be produced in order to fine-tune dosing by age and/or weight. These tablets can be scored (shaped with break-marks to allow easy division into two or four equally-sized parts) to provide further dosing flexibility. Unfortunately no second-line dispersible TB tablets exist today. We review here the main obstacles that prevent the development of such formulations and how these problems could be tackled successfully.

DEFINING THE NEEDS

Policy and dosing guidelines

One of the key difficulties in developing dispersible tablet formulations of second-line TB medications is the absence of pediatric dosing guidance. Simple allometric scaling and extrapolating exposure as measured in adults to children usually will not do, due to adult/child differences in gastric emptying and pH, gastrointestinal tract permeability in absorption surface area, expression of some drug transporters, biliary function, drug metabolism and renal clearance (6). As a consequence, the required absolute drug dose in children may vary 100-fold (7) and it is therefore dangerous to assume that exposure will be comparable (can simply be scaled) even between older and younger children. Because of well-established differences between older and younger children and infants, the International Conference of Harmonization (8) has recommended to divide childhood in five phases with respect to clinical drug use. Establishing pediatric exposure will therefore require dedicated clinical studies. Once age-dependent dosing

requirements have been established, dispersible tablets can be scored, or can be manufactured in a small set of easily distinguishable shapes and strengths in order to accommodate those dosing requirements. Established dosing guidelines are essential before the regulatory authorities can approve the submitted information package for the dispersible tablets for registration and approval. Dosing guidelines have recently been specified for first-line TB drugs for drug-susceptible TB but to date there are no such recommendations for MDR-TB.

Stability and compatibility challenges with dispersible formulations

A dispersible tablet has to meet the specifications of the disintegration test (dispersal under 3 minutes under specified conditions) and "fineness of dispersion test" (dispersed powder should pass through a 710 μM pore aperture sieve)(9). A common approach to generating dispersible tablets is the inclusion of high amounts of disintegrants such as sodium starch glycollate, microcrystalline cellulose; crospovidone and/or croscarmellose, excipients which swell upon contact with moisture and help disintegrate the tablet. The problem with many of these excipients is that they are highly hygroscopic (moisture absorbing), resulting in the spontaneous softening and swelling of the tablets over time. Moreover, most of the high-TB burden countries have high temperature and humidity storage conditions. Dedicated manufacturing procedures and special packaging can reduce the risks of moisture ingress using for example, double-aluminum blisters. When flavorings and sweeteners are added it is important to exclude the risk for interaction with the API(s); this means that long-term stability studies are necessary. Finally, all other excipient components in the mix are to be thoroughly evaluated in combination for compatibility issues with the API. For example, the binding of quinolone antibiotics to divalent cations has been well-documented (10).

Taste masking

The second-line anti-TB drugs that are available today comprise only a small set of chemical classes and most have highly bitter and obnoxious taste, for which children in particular have low tolerance. It is critical that these medicines, as used for children, are effectively taste-masked and in addition contain child-adapted flavors. Poor palatability of medications has been shown to negatively impact on treatment adherence in children (11), which in TB could result in treatment

failure, promote the emergence and spread of resistant MDR-TB, and waste resources. Today's anti-TB APIs are soluble and rapidly released, which tends to overwhelm taste-masking and flavoring efforts. One strategy to mask the drug's taste involves adsorbing the drug on to a complex forming agent (12, 13). This can be achieved using ion-exchange resins that release their ligands at increased pH (upon entry in the duodenum). However these resins tend to display an unreliable ligand-release rate, complicating drug exposure. Similarly the API may be complexed with cyclodextrins, but those are required in large quantities thereby increasing tablet size and manufacturing costs. Lastly, barrier coating can be used, whereby the contact of the API and taste receptors is minimized with the use of insoluble polymers. Various manufacturing techniques are available to achieve such a formulation, for example spray drying, bottom spray, solvent evaporation and others. These techniques demand the use of specialized equipment to achieve a good barrier coat; moreover these coatings may affect the API's release and exposure. Therefore, taste masking needs to be balanced with achieving effective drug release, and this process requires extensive experimentation; in most cases, changes in exposure that result from different formulations will need to be formally evaluated in pharmacokinetic studies in children.
Work on taste masking should be planned for and performed during the product development stage. Once a product is approved, significantly changing the composition requires extensive stability testing (two years or more). The early use of tools like the “artificial tongue” (14) and well-planned taste testing panels (involving children) would pay generous dividends.

Bioequivalence studies

Dispersible tablets represent an alternate solid dosage form to the existing immediate-release tablets. As previously mentioned, dispersible tablets contain different excipients and they tend to release the API earlier. Therefore, bioequivalence studies are required to characterize the rate and extent of API absorption and compare it to a comparator product representing the currently available dosage form. The pediatric dispersible tablet will contain a substantially lower amount of API compared to the currently available adult formulation. Therefore, multiple dispersible tablets must be administered and compared with a single adult immediate-release tablet, or in some cases with multiple immediate-release tablets to achieve dose equivalency. The different

release characteristics of the APIs from the formulations, combined with the different number of tablets result in a complex bioequivalence evaluation scenario. Failure to properly evaluate all these parameters may trigger requirements for further clinical efficacy studies conditional to successful registration. Timely development and acceptance of dosing guidelines and a decision on the appropriate comparator products may facilitate the process.

Fixed-dose combinations

All TB regimens today involve multiple drugs; combining these as fixed-dose combinations (FDCs) is highly desirable, mostly for reasons of patient adherence. However, the development of FDCs complicates the previously described challenges even further, making this task even more formidable for most combinations. Another problem is that the combination ratio is indeed 'fixed'; if the planned combination consists of one drug that is given at a single dose to all populations but a second one that requires finely tuned age- or weight-based dosing adjustments then such a FDC cannot be designed (or multiple FDCs may have to be designed wherein one drug is kept at a constant dose and the other one is varied). Ideally, FDC dispersible tablets are manufactured that can be dosed in multiples to meet the requirements of the different age groups. Dosing guidelines become a critical factor to decide on the quantities of each API in dispersible tablets. Even in its simplest form, formulating a FDC tablet in which the APIs are uniformly distributed is challenging, and is further complicated by suitable taste-masking strategies. There is also the risk that the APIs themselves may interact. Physical interactions between the first-line TB drugs have been well documented (12, 13). This can be overcome by designing bi-layered tablets, which are FDC tablets where the APIs are deposited in layers (15). However the manufacture of stably formulated bi-layered tablets is challenging and may require special equipment and multiple trials. Finally, bioequivalence must be demonstrated for each API and compared to the individual pharmacokinetics that was seen in clinical efficacy studies; this may fail if the drugs have different release profiles. Given the rapidly evolving TB treatment landscape, pursuing pediatric FDCs of second-line drugs may be challenging.

LESSONS FROM DEVELOPMENT OF DISPERSIBLE AND FIXED-DOSED COMBINATIONS FOR FIRST-LINE PEDRIATIC TB TREATEMENTS

For first-line treatment of pediatric TB, dispersible tablets and FDCs have already been developed, overcoming the challenges listed above. Most of the dispersible FDCs include rifampicin. One of the biggest hurdles in developing these was how to overcome the stability problems associated with the combination of rifampicin and isoniazid. These APIs tend to generate a complex (12, 13) that results in a reduction in rifampicin bioavailability. Problems associated with other APIs stem from hygroscopicity (a tendency to absorb water) of ethambutol, problematic divisibility of scored isoniazid/rifampicin dispersible tablets and other difficulties. Other challenges included taste-masking and bioequivalence when comparing with reference (comparator) capsules or film-coated tablets.

Progress in this area of development was made thanks to the productive collaboration between funders, regulators, manufacturers and the TB Alliance. Creative solutions like adding rifampicin later in the blend of ingredients thus minimizing the contact with isoniazid and moisture, and the judicious selection of packaging materials have helped create elegant drug products. These products are tested to the very high standards under varying storage conditions. Many of the hard-earned lessons learned in above undertakings will instruct future efforts in developing pediatric dispersible tablets for second-line TB medications.

Literature Rivew:

1. Arora et al., **(International publication number: WO 00/076479 Gazette 2000/51, 2000),** the present invention relates to taste masked compositions for bitter drugs, comprising a combination of two enteric polymers, such as a methacrylic acid copolymer, and a phthalate polymer. It also relates to a process for preparing such a composition.[18]

2. Jakobet al., (**International publication number: WO 2006/106023,2006**) The invention relates to the use of hydroxydeoxybenzoins (i.e. hydroxyl-substituted 1,2 diphenylethanones), salts thereof and mixtures thereof to mask or reduce unpleasant taste impressions, in particular bitter, astringent and/or metallic taste impressions. The invention

relates also to specific preparations comprising an effective amount of the designated hydroxydeoxybenzoins, salts thereof or mixtures thereof.[19]

3. Mertin et al., **(US publication number: US 2006/0177414 A1, 2006)** The Present invention relates to pharmaceuticals preparation for oral administration, comprising one or more active substance bound to an ion exchanger. In order to improve physical stability and acceptance, particularly in animals, a Pseudoplastic gel former thickener is induced.[20]

4. Khan et al. (2006) the purpose of this research was to mask the intensely bitter taste of Ondansetron HCl and formulate a rapid disintegrating tablet of the taste masked drug. Taste masking was done by complexing Ondansetron HCl with amino alkyl methacrylate copolymer (Eudragit EPO) in different ratios by the precipitation Method.[21]

5. Pilgaonkar et al. **(Patent number: US 8,545,890 B2, 2013)**The present invention describes a directly compressible composite excipient prepared by coating calcium silicate With a carbohydrate. The present invention further describes the incorporation of the composite excipient into a tablet formulation. The orally disintegrating tablets are of optimal mechanical strength and disintegrate Within 60 seconds in the oral cavity.[22]

6. Sing Romi et al **(International publication number WO 2005/020998 A1)**The field of the invention relates to pharmaceutical compositions of Moxifloxacin. The invention also relates to processes for the preparation of such compositions.[23]

3. BACKGROUND

Inconvenience in swallowing conventional solid dosage forms like tablets and capsules is a common problem in geriatric and pediatric patients. It is also difficult to swallow tablets in situation where water is not available, motion sickness and sudden episodes of coughing during the common cold, allergic condition and bronchitis. The goal of designing dispersible tablets is to avoid the risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction, thus providing improved safety, improved convenience

of administration, improved bioavailability and produce rapid onset of action. It also aims at avoiding swallowing problems and thereby enhances patient compliance.

4. RATIONALE OF STUDY:

Globally there are a growing number of children accessing second-line anti-tuberculosis medications for multidrug-resistant tuberculosis (TB), however there are very few child-friendly formulations. When used in pediatric medicine, dispersible tablets offer distinct advantages over liquid formulations and other approaches. This is particularly relevant for TB, where good stability, long shelf-life, and reduced costs for manufacturing, transport and storage are all critical to ensuring that drugs are accessible and affordable. In addition, fixed-dose combinations that reduce the pill burden and provide adequate taste masking may promote long-term adherence to TB treatment and prevention regimens for children that may last many months. Partial adherence may result in treatment failure and may also lead to the further selection and spread of resistant bacteria.

5. PLAN OF WORK

5.1 Preformulation

5.1.1 APIs studies

- Description, Solubility, LOD (Loss on Drying)
- Bulk density, Assay

5.1.2 APIs studies from IP, USP and BP

- Category
- Identification Test
- Assay

5.1.3 Testing of APIs

- Polymorph- X-ray diffraction method.
- Particle size distribution- Sieve Analysis method
- LOD - Thermal gravimetric method
- Assay- HPLC
- Bulk density- Tapping method

5.1.4 Excipients Interaction Studies

- Drug excipients interaction

5.2 Formulation

- Taste masking
- Wet granulation Process (Aqueous or Non Aqueous)
- Prelubrication
- Lubrication
- Tableting

5.3 Evaluation of formulation

- Physical appearance, colour, odour, taste
- Flow property- Carr's Compressibility and Angle of repose.
- Assay- HPLC Method
- Dissolution- Dissolution test apparatus
- Moisture content by KF

- Dispersibility Analysis
- Disintegration time

5.4 Packaging configuration

- Suitable packaging configuration evaluation

5.4 Stability Studies

- Schedule of Stability study, No. of Station, Storage condition

  Condition- Accelerated stability studies at 40 ± 2^0C / 75 ± 5% RH for 0,1,3,6 months and Room temperature studies at 25 ± 2^0C / 60 ± 5% RH for 3,6 months by using ICH guideline
- Test during stability studies

6. DURATION OF WORK:

Sr.	WORK	PERIOD
1	Literature review	6 Months
2	Selection and procurement of required drugs and excipients	6 Months
3	Characterization of procured drugs and excipients.	6 Months
4	Pre-formulations Study	4 Months
5	Development of dispersible tablets	8 Months
6	Evaluation of dosage forms	6 Months
	Total duration of project	**36 Months**

7. RESEARCHOUTCOME:

While challenging, much can be learned from earlier reformulation successes for first-line TB treatments and this can be used to guide development of subsequent formulations; their successful development also illustrates how the process can be driven by productive partnerships. However for most second-line TB treatments there remain many knowledge gaps for their use in children, especially regarding optimal dosing (16). It is of the greatest importance that existing clinical trials and formulation efforts already take into account how the new regimens can be administered to children, and that, at the very least, adequate data on adult drug exposure is available to guide subsequent pediatric formulation development. The need for pediatric formulations (17) and in particular the development of dispersible tablets for the treatment of TB in children is however a medical necessity. Because most TB APIs have an unpleasant taste yet must be taken over many months, the importance of developing taste-masked dispersible tablets for children remains a high priority, forming an essential link in the chain that runs from patient detection and diagnosis and drug access to adherence and treatment success.

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